(12) UK Patent Application (19) GB (11) 2 168 347 A

(43) Application published 18 Jun 1986

(21) Application No 8530591

(22) Date of filing 12 Dec 1985

(30) Priority data

(31) 8431426 (32) 13 Dec 1984 (33) GB

(71) Applicant
Glaxo Group Limited (United Kingdom),
Clarges House, 6-12 Clarges Street, London W1Y 8DH

(72) Inventors
David Edmund Bays
Colin Frederick Webb

(74) Agent and/or Address for Service
Elkington and Fife, High Holborn House, 52-54 High Holborn, London WC1V 6SH

(51) INT CL[4]
C07D 209/18 A61K 31/405 31/415 C07D 233/88 403/12 //
(C07D 403/12 209:18 295:12)

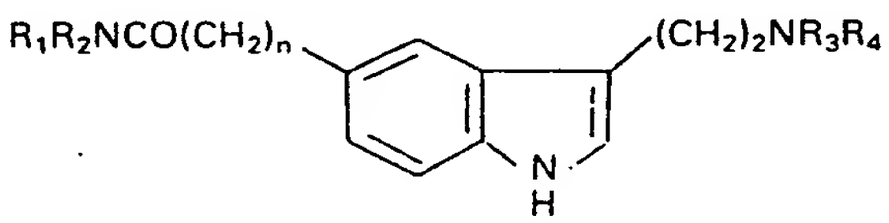
(52) Domestic classification (Edition H):
C2C 1341 1343 1414 200 213 215 220 226 22Y 246 247 250 251 252 25Y 280 281 282 28X 29X 29Y 305 30Y 313 31Y 321 322 323 328 32Y 338 342 34Y 351 352 364 36Y 493 574 57Y 584 594 604 620 624 62X 630 650 660 662 720 802 80Y AA KH KJ KZ MG
U1S 2415 C2C

(56) Documents cited
GB A 2082175

(58) Field of search
C2C

(54) Indoles

(57) Novel indoles of the general formula (I):



(I)

wherein
R_1 represents hydrogen, alkyl, cycloalkyl, alkenyl, phenyl or phenyl alkyl in which the phenyl ring may be unsubstituted or substituted by one or two substituents selected from alkoxy, hydroxy, halogen, a group R_5R_6NCO– where R_5 and R_6 each represents hydrogen or alkyl, or a group R_7R_8N–, where R_7 and R_8 each represents hydrogen or alkyl, or R_7R_8N– represents a saturated monocyclic 5– to 7– membered ring;
R_2 represents hydrogen or alkyl; or
R_1 and R_2 together with the nitrogen atom form a saturated monocyclic 5– to 7–membered ring;
R_3 and R_4 each represents hydrogen, alkyl or a 2-propenyl group; and
n is an integer from 2 to 5;
and physiologically acceptable salts and solvates thereof have selective vasoconstrictor activity and are useful in treating and/or preventing pain resulting from dilatation of the cranial vasculature, in particular migraine.

GB 2 168 347 A

SPECIFICATION

Indoles

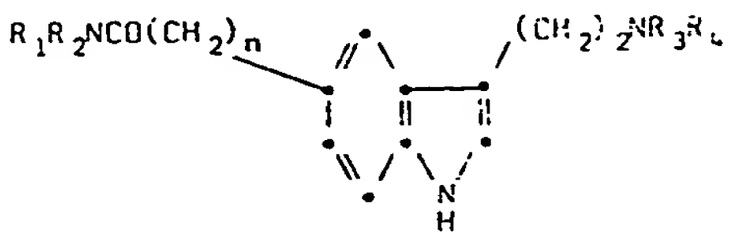
This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

The pain of migraine is associated with excessive dilatation of the cranial vasculature, and known treatments for migraine include the administration of compounds having vasoconstrictor properties, such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and dangerous side effects. Migraine may also be treated by administering an analgesic, usually in combination with an antiemetic, but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

We have now found a group of indole derivatives having potent and selective vasoconstrictor activity.

The present invention provides an indole of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom, C_{1-6}alkyl, C_{3-7} cycloalkyl or C_{3-6}alkenyl group, or a phenyl or phenyl (C_{1-4}) alkyl group in which the phenyl ring may be unsubstituted or substituted by one or two substituents selected from C_{1-3} alkoxy, hydroxy, halogen, a group R_5R_6NCO-, where R_5 and R_6 (which may be the same or different) each represents a hydrogen atom or a C_{1-3} alkyl group, or a group R_7R_8N- where R_7 and R_8 (which may be the same or different) each represents a hydrogen atom or a C_{1-3} alkyl group, or R_7R_8N- represents a saturated monocyclic 5- to 7- membered ring;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group; or R_1 and R_2 together with the nitrogen atom to which they are attached form a saturated monocyclic 5- to 7- membered ring;

R_3 and R_4 which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group, or a 2-propenyl group; and

n is an integer from 2 to 5; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The invention includes within its scope all optical isomers of compounds of formula (I) and their mixtures including the racemic mixtures thereof. All geometric isomers of compounds of general formula (I) are also included within the scope of the invention.

Referring to the general formula (I), the alkyl groups may be straight chain or branched chain alkyl groups, such as methyl, ethyl or isopropyl groups. The cycloalkyl group may be for example a cyclopentyl or cyclohexyl group. Alkenyl groups which may be represented by R_1 include propenyl and butenyl groups. It will be appreciated that the double bond in such alkenyl groups will not be adjacent to the nitrogen atom.

When R_1 represents a substituted phenyl or substituted phenyl (C_{1-4}) alkyl group a C_{1-3} alkoxy substituent may be for example methoxy, and a halogen substituent may be for example fluorine, chlorine or bromine. Substituents of the formula R_5R_6NCO- include N-methylcarbamoyl and examples of the substituents R_7R_8N- include amino, dimethylamino and pyrrolidino. The substituent may be in the ortho, meta or para position.

The alkyl moiety of the phenyl (C_{1-4}) alkyl group may be, for example, a methyl or ethyl moiety.

A preferred class of compounds represented by general formula (I) is that wherein R_1 represents a hydrogen atom, a C_{1-6} alkyl or C_{3-6} alkenyl group, or a phenyl or phenyl (C_{1-4}) alkyl group in which the phenyl ring may be substituted as previously described.

In the compounds of general formula (I) it is preferred that one of R_1 and R_2 represents a hydrogen atom.

A further preferred class of compounds is that wherein R_3 and R_4, (which may be the same or different) each represents a hydrogen atom or a C_{1-3} alkyl group.

Another preferred class of compounds according to the invention is that wherein n is 2 or 3.

When R_1 represents a substituted phenyl or substituted phenyl(C_{1-4}) alkyl group, preferred substituents include C_{1-3} alkoxy (e.g. methoxy), halogen (e.g. chlorine), a group R_5R_6NCO-, or a group R_7R_8N-. When the substituent is a group R_5R_6NCO- it is particularly preferred that R_5 and R_6 independently represent a hydrogen atom or a methyl group. When the substituent is a group R_7R_8N-, R_7 and R_8 (which may be the same or different) preferably represent a hydrogen atom or a methyl group or together form a pyrroli-

dino ring.

A particularly preferred class of compounds falling within the scope of general formula (I) is that wherein R_1 represents a C_{1-3} alkyl group (e.g. methyl), a C_{3-6} alkenyl group (e.g. 2-propenyl) or a phenyl (C_{1-2}) alkyl group, in which the phenyl ring may be unsubstituted or substituted as previously described; R_2 represents a hydrogen atom; R_3 and R_4 (which may be the same or different) each represents a hydrogen atom or a methyl or ethyl group; and n is 2 or 3; and their physiologically acceptable salts and solvates (e.g. hydrates).

Preferred compounds according to the invention include:-

3-(2-aminoethyl)-*N*-(phenylmethyl)-1*H*-indole-5-propanamide;

3-(2-aminoethyl)-*N*-([4-(-1-pyrrolidinyl)phenyl]methyl)-1*H*-indole-5-propanamide;

3-[2-(dimethylamino)ethyl]-*N*[(4-methoxyphenyl)methyl]-1*H*-indole-5-propanamide;

3-(2-aminoethyl)-*N*-(2-propenyl)-1*H*-indole-5-propanamide;

3-(2-aminoethyl)-*N*-[(4-methoxyphenyl)methyl]-1*H*-indole-5-propanamide;

and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, nitrates, oxalates, phosphates, tartrates, citrates, fumarates, maleates, succinates, and sulphonates e.g. mesylates. Other salts may be useful in the preparation of compounds of formula (I) e.g. creatinine sulphate adducts.

It will be appreciated that the invention extends to other physiologically acceptable equivalents of the compounds according to the invention, i.e. physiologically acceptable compounds which are converted *in vivo* into the parent compound. Examples of such equivalents include physiologically acceptable, metabolically labile N-acyl derivatives.

Compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog, whilst having a negligible effect on blood pressure. The selective vasoconstrictor action of compounds of the invention has been demonstrated *in vitro*.

Compounds of the invention are useful in treating pain resulting from dilatation of the cranial vasculature, in particular migraine and cluster headache.

Accordingly, the invention also provides a pharmaceutical composition adapted for use in human medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcelluose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-*p*-hydroxybenzoates or sorbic acid). The liquid preparations may also contain conventional buffers, flavouring, colouring and sweetening agents as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents, and/or agents to adjust the tonicity of the solution. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for

use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, buccal or rectal administration to man (of average bodyweight e.g. about 70kg) for the treatment of migraine is 0.1 to 100mg of the active ingredient per unit dose which could be administered, for example, up to 8 times per day, more usually 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

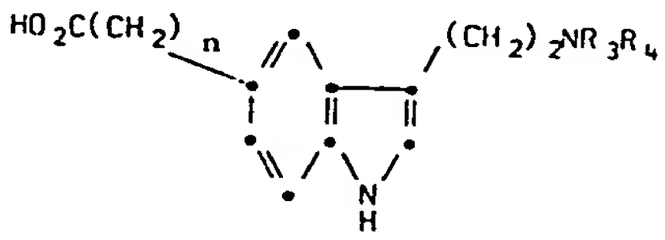
For oral administration a unit dose will preferably contain from 0.5 to 50mg e.g. 2 to 40mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 5mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 to 2mg of a compound of the invention and, each dose administered via capsules or cartridges in an inhaler or insufflator contains 0.2 to 20mg. The overall daily dose by inhalation will be within the range 1mg to 100mg. Administration may be several times daily, for example from 2 to 8 times, giving for example, 1, 2 or 3 doses each time.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants.

According to another aspect of the invention, compounds of formula (I), and physiologically acceptable salts or solvates (e.g. hydrates) thereof, may be prepared by the general methods outlined below. In the following processes, R_1, R_2, R_3, R_4 and n are as defined for the general formula (I) unless otherwise specified.

According to one general process (A), a compound of general formula (I) may be prepared by condensing an amine of formula R_1R_2NH with an acid of general formula (II):



(II)

or an acylating agent corresponding thereto, or a salt (for example an organic or inorganic acid addition salt such as the hydrochloride, hydrobromide, sulphate or maleate salt, or creatinine sulphate adduct) or a protected derivative thereof.

The reaction involving condensation of the amine HNR_1R_2 with the acid of general formula (II) is desirably conducted in the presence of a coupling agent, for example carbonyl diimidazole or a carbodiimide such as N,N'-dicyclohexylcarbodiimide. The condensation reaction may be carried out in a suitable reaction medium preferably an anhydrous medium, conveniently at a temperature of from −50 to +50°C, preferably −5 to +30°C. Suitable solvents include halogenated hydrocarbons e.g. dichloromethane, nitriles e.g. acetonitrile, amides e.g. N,N-dimethylformamide and ethers e.g. tetrahydrofuran, as well as mixtures of two or more such solvents. The reaction may also be carried out in the absence of a coupling agent in a suitable reaction medium such as a hydrocarbon (e.g. toluene or xylene) conveniently at a temperature of from 50 to 120°C.

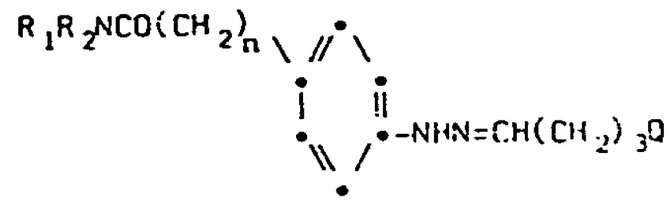
Acylating agents corresponding to the acid of general formula (II) which may be employed in the preparation of compounds of formula (I) include acid halides, for example acid chlorides. Such acylating agents may be prepared by reaction of an acid of general formula (II), or a salt or protected derivative thereof, with a halogenating agent such as phosphorus pentachloride, thionyl chloride or oxalyl chloride. Other suitable acylating agents which may be employed in the preparation of compounds of formula (I) include alkyl esters such as the methyl ester, activated esters (e.g. the 2-(1-methylpyridinyl) ester) and mixed anhydrides (e.g. formed with pivaloyl chloride, a sulphonyl halide such as methanesulphonyl chloride or a haloformate, such as a lower alkylhaloformate). Acids of formula (II) may themselves be prepared for example by cyclisation of an appropriate hydrazine compound, in an analogous manner to process (B) described hereinafter.

When an acylating agent corresponding to the acid of general formula (II) is employed the condensation process may be effected in aqueous or non-aqueous reaction media and conveniently at a temperature of from −70 to +150°C. Thus the condensation reaction using an acid halide, anhydride or activated ester may be effected in a suitable reaction medium such as an amide e.g. N,N-dimethylformamide, an ether e.g. tetrahydrofuran or diethylether, a nitrile e.g. acetonitrile, a halogenated hydrocarbon e.g. dichloromethane, or mixtures thereof, optionally in the presence of a base such as a tertiary amine e.g. triethylamine or pyridine and preferably at a temperature of from −5 to +25°C. The condensation reaction using an alkyl ester may be effected in a suitable reaction medium such as an alcohol e.g. methanol, an amide e.g. dimethylformamide, an ether e.g. tetrahydrofuran or diethylether, or mixtures thereof and conveniently at a temperature of from 0 to 100°C. In some instances, the amine HNR_1R_2 may itself act as the reaction solvent.

Where it is desired to prepare a compound of formula (I) in which R_1 and R_2 are both hydrogen the condensation may be effected using ammonia, which may for example be employed in the form of aqueous ammonia or in a solvent such as methanol.

Compounds of general formula (II) and acylating agents corresponding thereto, such as the alkyl esters, are novel compounds and constitute a further aspect of the present invention.

According to another general process (B), compounds of formula (I) may be prepared by the cyclisation of a compound of general formula (III):



(III)

wherein Q is the group NR_3R_4 (or a protected derivative thereof) or a leaving group such as a halogen atom (e.g. chlorine or bromine) or an acyloxy group (e.g. a carboxylic or sulphonic acyloxy group such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, p-nitrobenzoyloxy, p-toluenesulphonyloxy or methanesulphonyloxy group).

The reaction may conveniently be effected in aqueous or non-aqueous reaction media, and at temperatures of from 20 to 200°C, preferably 50 to 125°C.

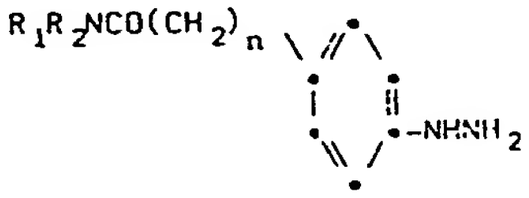
Particularly convenient embodiments of the process are described below.

When Q is the group NR_3R_4 (or a protected derivative thereof) the process is desirably carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons 1967).

Alternatively the cyclisation may be carried out in an aqueous or non-aqueous reaction medium, in the presence of an acid catalyst. When an aqueous medium is employed this may be an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents, and the acid catalyst may be for example, an inorganic acid such as concentrated hydrochloric or sulphuric acid or an organic acid, such as acetic acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise one or more ethers (e.g. as previously described) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride.

When Q is a leaving group such as a chlorine or bromine atom the reaction may be effected in an aqueous organic solvent, such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) in the absence of an acid catalyst conveniently at a temperature of from 20 to 200°C, preferably 50 to 125°C. This process results in the formation of a compound of formula (I) wherein R_3 and R_4 are both hydrogen atoms.

According to a particular embodiment of this process compounds of formula (I) may be prepared directly by the reaction of a compound of general formula (IV):



(IV)

or a salt thereof,

with a compound of formula (V):

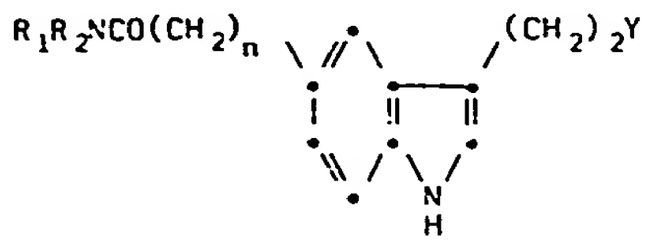
$$OCH(CH_2)_3Q \quad (V)$$

(wherein Q is as defined above) or a salt or protected derivative thereof (such as an acetal or ketal e.g. formed with an appropriate alkyl orthoformate or diol, or protected as a bisulphite addition complex) using the appropriate conditions as described above for the cyclisation of compounds of general formula (III). It will be appreciated that in this embodiment of the cyclisation process (B) a compound of general formula (III) is formed as an intermediate, and may be reacted *in situ* to form the desired compound of general formula (I).

Compounds of general formula (III) may, if desired, be isolated as intermediates during the process for the preparation of compounds of formula (I) wherein a compound of formula (IV), or a salt or protected derivative thereof, is reacted with a compound of formula (V), or a salt or protected derivative thereof, in a suitable solvent, such as an aqueous alcohol (e.g. methanol) at a temperature of, for example, 20 to 30°C. If an acetal or ketal of a compound of formula (V) is used, it may be necessary to carry out the reaction in the presence of an acid (for example, acetic or hydrochloric acid).

Compounds of general formula (IV) may be prepared for example from the corresponding nitro compounds, using conventional procedures.

A further general process (C) for preparing compounds of general formula (I) involves reacting a compound of general formula (VI):



(VI)

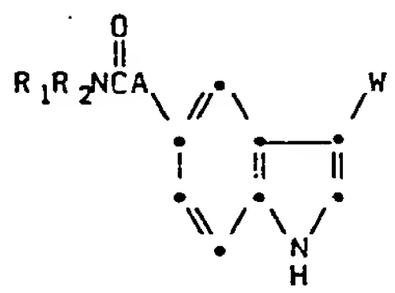
(wherein Y is a readily displaceable group) or a protected derivative thereof, with an amine of formula R_3R_4NH.

The displacement reaction may conveniently be carried out on those compounds of formula (VI) wherein the substituent group Y is a halogen atom (e.g. chlorine, bromine or iodine) or a group OR_9 where OR_9 is, for example, an acyloxy group which may be derived from a carboxylic or sulphonic acid, such as an acetoxy, chloroacetoxy, dichloroacetoxy, trifluoroacetoxy, p-nitrobenzoyloxy, p-toluenesulphonyloxy or methanesulphonyloxy group.

The displacement reaction may be conveniently effected in an inert organic solvent (optionally in the presence of water), examples of which include alcohols, e.g. ethanol; cyclic ethers, e.g. dioxan or tetrahydrofuran; acylic ethers e.g. diethylether; esters, e.g. ethyl acetate; amides, e.g. N,N-dimethylformamide; and ketones e.g. acetone or methylethyl ketone, at a temperature of from −10 to +150°C, preferably 20 to 50°C.

The compounds of general formula (VI) wherein Y is a halogen atom may be prepared by reacting a hydrazine of general formula (IV) with an aldehyde or ketone (or a protected derivative thereof) of formula (V) in which Q is a halogen atom, in an aqueous alkanol (e.g. methanol) containing an acid (e.g. acetic or hydrochloric acid). Compounds of formula (VI) wherein Y is the group OR_9 may be prepared from the corresponding compound wherein Y is a hydroxyl group by acylation or sulphonylation with the appropriate activated species (e.g. anhydride or sulphonyl chloride) using conventional techniques. The intermediate alcohol may be prepared by cyclisation of a compound of formula (III) wherein Q is a hydroxyl group (or a protected derivative thereof) under standard conditions.

Compounds of formula (I) may also be prepared by another general process (D) involving reduction of a compound of general formula (VII):



(VII)

[wherein W is a group capable of being reduced to give the required $-(CH_2)_2NR_3R_4$ group or to give a protected derivative of $-(CH_2)_2NR_3R_4$ and A represents the group $-(CH_2)_n-$ as herein defined or a group capable of being reduced to $-(CH_2)_n-$] or a salt or protected derivative thereof.

The required $-(CH_2)_2-$ and $-NR_3R_4$ groups at the 3- position may be formed by reduction steps which take place separately or together in any appropriate manner.

Groups A which may be reduced to give the required group $-(CH_2)_n-$ include corresponding unsaturated groups, such as C_{2-5} alkenyl groups.

Examples of groups represented by the substituent W include $-(CH_2)_2NO_2$; $-CH=CHNO_2$; $-(CH_2)_2N_3$; $-CH_2CN$; $-CH_2CHO$; $-COCH_2Z$; $-CH_2CH=NOH$; and $-CH(OH)CH_2NR_3R_4$; (wherein Z is an azido group or the group $-NR_3R_4$ or a protected derivative thereof).

Groups which may be reduced to the $-(CH_2)_2-$ moiety at the 3- position include the corresponding unsaturated group and corresponding groups containing a hydroxyl group or a carbonyl function.

Groups which may be reduced to the group $-NR_3R_4$ where R_3 and R_4 are both hydrogen include nitro, azido, hydroxyimino and nitrile groups. In the latter case, reduction yields the group $-CH_2NH_2$ and thus provides a methylene group of the $-(CH_2)_2-$ moiety.

The required $-NR_3R_4$ group wherein R_3 and/or R_4 are other than hydrogen may be prepared by reduction of a nitrile $-CH_2CN$ or an aldehyde $-CH_2CHO$ in the presence of an amine, R_3R_4NH.

A particularly suitable method for preparing a compound of formula (I) wherein R_3 and/or R_4 is other than hydrogen is reductive alkylation of the corresponding compound wherein R_3 and/or R_4 represent hydrogen with an appropriate aldehyde or ketone (e.g. formaldehyde or acetone) in the presence of a suitable reducing agent. In some instances (e.g. for the introduction of the group(s) R_4 and/or R_5 where these represent methyl) the aldehyde (e.g. formaldehyde) may be condensed with the amine and the intermediate thus formed may subsequently be reduced using a suitable reducing agent.

It will be appreciated that the choice of reducing agent and reaction conditions will be dependent on the nature of the group W, as well as the other groups already present on the molecule.

Suitable reducing agents which may be used in the above process for the reduction of compounds of formula (VII) wherein W represents, for example, the groups $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-(CH_2)_2N_3$, $-CH_2CN$, $-CH_2CH=NOH$ and $-CH(OH)CH_2NR_3R_4$ include hydrogen in the presence of a metal catalyst, for example Raney Nickel or a noble metal catalyst such as platinum, platinum oxide, palladium, palladium oxide or rhodium, which may be supported, for example, on charcoal, kieselguhr or alumina. In the case of Raney Nickel, hydrazine may also be used as the source of hydrogen. This process may conveniently be carried out in a solvent such as an alcohol e.g. ethanol, an ether, e.g. dioxan or tetrahydrofuran, an amide, e.g. dimethylformamide or an ester e.g. ethyl acetate, and at a temperature of from −10 to +50°C, preferably −5 to +30°C.

The reduction process may also be effected on compounds of formula (VII) wherein W represents, for example, the groups $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-(CH_2)_2N_3$, $-CH(OH)CH_2NR_3R_4$ or $-COCH_2Z$ (where Z is as previously defined), using an alkali metal or alkaline earth metal borohydride or cyanoborohydride e.g. sodium or calcium borohydride or cyanoborohydride which process may conveniently be carried out in an alcohol such as propanol or ethanol, or a nitrile such as acetonitrile, and at a temperature of from 10 to 100°C, preferably 50 to 100°C. In some instances the reduction using a borohydride may be carried out in the presence of cobaltous chloride.

Reductive alkylation of a compound of formula (VII) may be effected using an alkali metal or alkaline earth metal borohydride or cyanoborohydride. The reaction may be effected in an aqueous or non-aqueous reaction medium, conveniently in an alcohol (e.g. methanol or ethanol) or an ether (e.g. dioxan or tetrahydrofuran) optionally in the presence of water. The reaction may conveniently be carried out at a temperature in the range 0 to 100°C, preferably 5 to 50°C.

A particular embodiment of general process (D) includes the reduction of a compound of formula (VII) wherein W is the group $-CH_2CN$, for example by catalytic reduction with hydrogen in the presence of a catalyst such as palladium on charcoal or rhodium on alumina, optionally in the presence of an amine HNR_3R_4. The reduction may be effected in a suitable solvent such as an alcohol e.g. methanol or ethanol.

A compound of general formula (I) where R_4 is a hydrogen atom may also be prepared by hydrogenolysis of a corresponding compound wherein R_4 is a benzyl group, e.g. with hydrogen in the presence of a catalyst, e.g. 10% palladium on carbon.

Suitable reducing agents which may be used in the reduction of the group A include hydrogen in the presence of a metal catalyst. Appropriate metal catalysts and conditions for the reduction process are as described for the reduction of the group W.

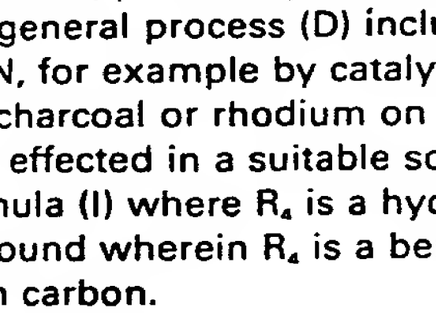
The starting materials or intermediate compounds of formula (VII) wherein W represents $-(CH_2)_2NO_2$, $-CH=CHNO_2$, $-CH_2CN$ or $-COCH_2Z$ may be prepared by analogous methods to those described in UK Published Patent Application No. 2035310, and 'A Chemistry of Heterocyclic Compounds - Indoles Part II', Chapter VI, edited by W. J. Houlihan (1972) Wiley Interscience, New York.

Compounds of formula (VII), wherein W is the group $-CH_2CHO$ may be prepared by oxidation (e.g. with Jones' reagent) of a compound of formula (VI) wherein Y is a hydroxyl group. A compound of formula (VII) wherein W is the group $-CH_2CH=NOH$ may be prepared by treatment of the corresponding aldehyde with hydroxylamine hydrochloride using standard conditions.

The intermediate compound of formula (VII) wherein W is the group $-(CH_2)_2N_3$ may be prepared from a compound of formula (VI) wherein Y is a halogen atom using standard procedures.

Standard reducing agents such as sodium borohydride may be used to prepare a compound of formula (VII) wherein W is the group $-CH(OH)CH_2NR_3R_4$ from the corresponding compound of formula (VII) wherein W is the group $-COCH_2NR_3R_4$.

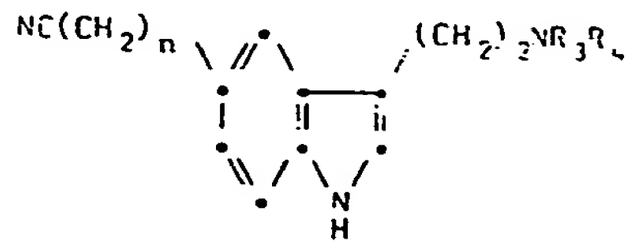
The intermediate compounds of formula (VII) wherein A represents a C_{2-5} alkenyl group may be prepared by reacting a compound of general formula (VIII)



(VIII)

(wherein W is as defined for general formula (VII) and p is zero or an integer of from 1 to 3) with, for example, an appropriate phosphonium salt, using standard conditions.

Compounds wherein R_1 and R_2 are both hydrogen atoms may be prepared according to a further general process (E) which comprises reacting a nitrile of general formula (IX):



(IX)

or a salt or protected derivative thereof, with a suitable oxygen containing compound. Thus, for example, a nitrile of general formula (IX) may be hydrolysed with an acid or an alkali under controlled conditions. Acids and alkalis which may be employed in this process include concentrated sulphuric acid; concentrated hydrochloric acid; a mixture of concentrated sulphuric acid, acetic acid and water (1:1:1); polyphosphoric acid; sodium *t*-butoxide in refluxing t-butanol; sodium hydroxide in aqueous ethanol in the presence of hydrogen peroxide; a base in the form of a resin; or boron trifluoride in acetic acid. The reaction may conveniently be effected at temperatures of from −10 to 100°C.

Compounds of general formula (IX) may themselves be prepared for example by cyclisation of the appropriate hydrazone, in an analogous manner to process (B).

According to a further general process (F) a compound of formula (I) according to the invention, or a salt or protected derivative thereof, may be converted into another compound of formula (I) using conventional procedures.

For example, a compound of general formula (I) wherein one or more of R_1, R_2, R_3 and R_4 are alkyl groups may be prepared from the corresponding compounds of formula (I) wherein one or more of R:i1, R_2, R_3 and R_4 represent hydrogen atoms, by reaction with a suitable alkylating agent such as a compound of formula R_xL, (where R_x represents the desired R_1, R_2, R_3 or R_4 group and L represents a leaving group such as a halogen atom or a tosylate group) or a sulphate $(R_x)_2SO_4$. Thus, the alkylating agent may be for example an alkyl halide (e.g. methyl or ethyl iodide), alkyl tosylate (e.g. methyl tosylate) or dialkylsulphate (e.g. dimethylsulphate).

The alkylation reaction may conveniently be carried out in an inert organic solvent such as an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides such as sodium or potassium hydride; alkali metal amides such as sodium amide; alkali metal carbonates such as sodium carbonate; alkali metal alkoxides such as sodium or potassium methoxide, ethoxide or t-butoxide; and tetrabutylammonium fluoride. When an alkyl halide is employed as the alkylating agent the reaction may also be carried out in the presence of an acid scavenging agent such as propylene or ethylene oxide. The reaction may be conveniently effected at a temperature of from −20° to 100°C.

Compounds of formula (I) wherein R_1 represents a cycloalkyl, alkenyl or phenylalkyl group and/or one or both of R_3 and R_4 represents propenyl may be prepared similarly, using an appropriate compound of formula R_xL or $(R_x)_2SO_4$.

According to another general process (G), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the reaction sequence for the preparation of a compound of general formula (I) or a salt thereof it may have been necessary or desirable to protect one or more sensitive groups in the molecule to avoid undesirable side reactions. For example it may be necessary to protect the group NR_3R_4, wherein R_3 and/or R_4 represents hydrogen, by protonation or with a group easily removable at the end of the reaction sequence. Such groups may include, for example, aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl; or acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl.

In some cases, it may also be desirable to protect the indole nitrogen with, for example, an aralkyl group such as benzyl.

Subsequent cleavage of the protecting group or groups may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal) or sodium and liquid ammonia; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation. The phthaloyl group may be removed by hydrazinolysis (e.g by treatment with hydrazine hydrate) or by treatment with a primary amine (e.g. methylamine).

As will be appreciated, in some of the general processes (A) to (F) described previously it may be necessary or desirable to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt therof may be carried out subsequent to any of the previously described processes (A) to (F).

Thus, according to a further aspect of the invention, the following reactions in any appropriate sequence may if necessary and/or desired be carried out subsequent to any of the processes (A) to (F):

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate (e.g. hydrate) thereof.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I), with an appropriate acid, pref-

erably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

The starting materials or intermediate compounds for the preparation of the compounds according to this invention may be prepared by analogous methods to those described in UK Published Patent Application No. 2035310.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5- position may be introduced before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples. All temperatures are in °C.

Chromatography was carried out either in the conventional manner using silica gel (Merck, Kieselgel 60, Art. 7734 or 7747) or by flash chromatography (W. C. Still, M. Kahn and A. Mitra, J. Org. Chem. 1978, *43*, 2933) on silica (Merck 9385) and thin layer chromatography (t.l.c.) on silica (Macherly-Nagel, Polygram) except where otherwise stated. The following abbreviations define the eluent used for chromatography and t.l.c.

A)	Dichloromethane-ethanol-0.88 ammonia	50:8:1
B)	Dichloromethane-ethanol-0.88 ammonia	35:8:1
C)	Dichloromethane-ethanol-0.88 ammonia	25:8:1
D)	Dichloromethane-ethanol-0.88 ammonia	40:8:1
E)	Dichloromethane-ethanol-0.88 ammonia	20:8:1
F)	Dichloromethane-ethanol-0.88 ammonia	100:8:1
G)	Dichloromethane-ethanol-0.88 ammonia	75:8:1
H)	Ethyl acetate-cyclohexane-acetic acid	2:4:1
I)	Ethyl acetate-ethanol-water-0.88 ammonia	25:15:1:1
J)	Ethyl acetate-ethanol-water-0.88 ammonia	25:15:8:2
K)	Toluene-ethanol-0.88 ammonia	78:20:2
L)	Dichloromethane-ethanol-0.88 ammonia	78:20:2
M)	Dichloromethane-ethanol-0.88 ammonia	200:8:1
N)	Toluene-ethanol-0.88 ammonia	39:10:1

Intermediates were routinely checked for purity by t.l.c. employing u.v. light for detection and spray reagents such as potassium permanganate ($KMnO_4$). In addition indolic intermediates were detected by spraying with aqueous ceric sulphate (CeIV) and tryptamines by spraying with a solution of iodoplatinic acid (IPA) or ceric sulphate.

Proton (^1H) nuclear magnetic resonance (n.m.r.) spectra were obtained either at 90MHz using a Varian EM 390 instrument or at 250MHz using a Bruker AM or WM 250 instrument. s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br = broad.

Reactivials are 4ml stout-walled glass vials with a screw cap and teflon-faced disc, supplied by Pierce and Warriner (UK) Ltd.

The following abbreviations are used in Tables 1 and 2 hereinafter:

TEA - triethylamine
PC - pivaloyl chloride
EtOH - ethanol
MeOH - methanol
IPA - isopropanol
EtOAC - ethyl acetate
IPAC - isopropylacetate
CH - cyclohexane
BU - butan-2-one
AC - acetone
HH - hydrazine hydrate.

Intermediate 1

4-Hydrazinobenzenepropanoic acid hydrochloride

To a stirred suspension of 4-aminobenzenepropanoic acid (3.30g) in concentrated hydrochloric acid (25ml) was added a solution of sodium nitrite (1.45g) in water (10ml), at such a rate that the temperature did not exceed +3°. When the addition was complete, the solution was stirred at 0° for 10 min. The mixture was added to a stirred solution of tin (II) chloride dihydrate (22.5g) in concentrated hydrochloric acid (15ml) at −10°, at such a rate that the temperature did not exceed −5°. The resulting suspension was allowed to warm to room temperature over a period of 1h. The solid was collected by filtration, washed

with ethanol (50ml), ether (100ml) and dried *in vacuo* yielding the *title compound* as a powder (3.9g) m.p. 205-6°C (dec). Crystallisation from 2-propanol afforded an analytically pure sample m.p. 209-210° (dec).

Intermediate 2

3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-propanoic acid

A mixture of intermediate 1 (5.8g) and 2-(4,4-diethoxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (7.79g) was heated under reflux in water (150ml) containing acetic acid (50ml) for 2h. The cooled suspension was extracted with ethyl acetate (2 × 150ml), and the combined organic extracts were washed with water (100ml) and brine (100ml). Evaporation of the solvent gave a gum which was dissolved in ethyl acetate and adsorbed onto silica (30g). This was added to a column of silica and eluted (H). The appropriate fractions gave a powder which crystallised from ethyl acetate-cyclohexane [1:1] (100ml) to give the *title compound* as a powder (5.0g) m.p. 171-2°.

Intermediate 3

4-Hydrazinobenzenebutanoic acid, hydrochloride

To a stirred suspension of 4-aminobenzenebutanoic acid (5.37g) in concentrated hydrochloric acid (37.5ml) at −5° was added a solution of sodium nitrite (2.18g) in water (15ml) at such a rate that the temperature did not exceed +2°. When the addition was complete, the mixture was stirred for 10 min, and then added to a stirred solution of tin (II) chloride dihydrate (33.75g) in concentrated hydrochloric acid (25ml) at −10° at such a rate that the temperature did not exceed −5°. After stirring the resulting suspension for 30 min, the solid was collected by filtration, washed with ether (100ml) and dried. Crystallisation from ethanol (100ml) and isopropyl acetate (100ml) gave the *title compound* as a powder (3.13g) m.p. 199-201°.

Intermediate 4

3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-butanoic acid

A mixture of 4-hydrazinobenzenebutanoic acid (2.305g) and 2-(4,4-diethoxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (2.91g) was heated under reflux in water (112.5ml) and acetic acid (37.5ml) for 1h. The suspension was poured into ethyl acetate (150ml) and the phases were separated. The organic phase was washed with brine (50ml), dried (Na_2SO_4) and evaporated under reduced pressure yielding a gum. This was dissolved in tetrahydrofuran (30ml) and adsorbed onto silica (20g). The dried material was added to a column of silica and eluted (H). Appropriate eluates were collected and evaporated under reduced pressure. Trituration of the residue with cyclohexane gave the *title compound* as a powder (2.35g) m.p. 160-2°.

Intermediate 5

(E)-Methyl 3-[4-[2-[2-(2-oxo-3-piperidinylidine)]hydrazino]phenyl]-2-propenoate

To a suspension of (E)-methyl 3-(4-aminophenyl)-2-propenoate (10.68g) in water (150ml) and conc. hydrochloric acid (12.5ml) at 0-2° was added a solution of sodium nitrite (3.9g) in water (12.5ml). The mixture was stirred for 0.25h and a solution of 3-carbethoxy-2-piperidone (prepared from 3-carbethoxy-2-piperidone (8.55g) and potassium hydroxide (3.0g) in water (100ml) which was allowed to stand for 72h at 5°) was added. The reaction mixture was adjusted to pH 4-5 with sodium acetate, allowed to warm to room temperature, and stirred for 18h. The precipitated solid was collected, washed with ethanol and ether and dried at 60° in vacuo to give the *title compound* as a solid (13.0g) mp. 208-9°.

Intermediate 6

(E)-Methyl 3-(1,2,3,4-tetrahydro-1-oxo-9H-pyrido[3,4-b]indol-6-yl)-2-propenoate

Intermediate 5 (0.5g) in 85% aqueous formic acid was heated under reflux for 2h and allowed to cool to room temperature. The mixture was filtered to give the *title compound* as a crystalline solid (0.22g) m.p. 258-259°.

Intermediate 7

(E)-3-(2-Aminoethyl)-5-(2-carboxyl-1-ethenyl)-1H-indole-2-carboxylic acid

Intermediate 6 (2.0g) in a mixture of 60% aqueous ethanol (45ml) and potassium hydroxide (7.5g) was heated at 60° for 4h. The solution was cooled to 0° and treated dropwise with 20% hydrochloric acid to pH 5. The precipitate was filtered, washed with water, ethanol and ether and dried to give the *title compound* as a solid (1.7g) m.p. 292-295 dec.

Intermediate 8

3-(2-Aminoethyl)-5-(2-carboxyethyl)-1H-indole-2-carboxylic acid

Intermediate 7 (1.5g), 10% palladium oxide on carbon (200mg) and acetic acid (50ml) were hydrogenated at atmospheric pressure for 5.5h (hydrogen uptake 148ml). The reaction mixture was filtered, evaporated to dryness and crystallised from methanol/ether to give the *title compound* as a crystalline solid (1.1g) m.p. 230-232°.

Intermediate 9

3-(2-Aminoethyl)-1H-indole-5-propanoic acid

Intermediate 8 (0.9g) was heated at 100° in a mixture of acetic acid (27ml) and 20% aqueous hydrochloric acid for 60h. Evaporation to dryness gave the *title compound* as a crystalline solid (0.9g), which was used in the next stage without purification.

Intermediate 10

Ethyl-3-(2-aminoethyl)-1H-indole-5-propanoate, hydrochloride

Intermediate 9 (0.85g) was added to a mixture of thionyl chloride (10ml) in ethanol (40ml) under nitrogen. The reaction mixture was heated at reflux for 4h, cooled to 50° and ether (200ml) was added. Filtration and evaporation of the mother liquors to dryness gave an oil which was chromatographed on silica gel. Elution (I) gave the tryptamine which was converted into the hydrochloride salt in a mixture of ethanol and ether, to give the *title compound* as a crystalline solid (0.4g) m.p. 182-5°.

Intermediate 11

(E) and (Z)-Methyl 3-[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-2-propenoate

5-Bromo-N,N-dimethyl-1*H*-indole-3-ethanamine (2.14g) was heated at 100° in an autoclave with methyl acrylate (0.90ml) palladium (II) acetate (18mg) and tri(o-tolyl)phosphine (49mg) in dry triethylamine (4ml) for 17h. More palladium acetate (18mg) tri(o-tolyl)phosphine (100mg), methyl acrylate (0.9ml) and triethylamine (1.5ml) were added, and heating was continued at 100° for 16h. The mixture was partitioned between water (20ml) and ethyl acetate (20ml). The aqueous layer was extracted with ethyl acetate (2 × 20ml), and the organic layers were washed with brine (2 × 15ml), dried ($MgSO_4$) and evaporated to give the *title compound* as an oil (2.30g), contaminated with starting material. This material was used in the next stage without further purification.

Intermediate 12

Methyl 3-[2-(dimethylamino)ethyl]-1H-indole-5-propanoate

Intermediate 11 (2.08g) in ethanol (100ml) containing 2N hydrochloric acid (5ml) was hydrogenated at room temperature and pressure over 10% palladium oxide on charcoal (50% paste with water, 0.4g) until hydrogen uptake had ceased (28h; further 400mg portions of catalyst being added after 2h 20 min. and after 17h). After filtration of the catalyst, the solvent was evaporated and the residue basified with 8% aqueous sodium bicarbonate (40ml) and extracted with ethyl acetate (4 × 50ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give the *title compound* as an oil (1.69g).

T.l.c. (SiO_2) K Rf. 0.35 detection; u.v./IPA.

Intermediate 13

3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-carboxaldehyde, quarter hydrate

Raney nickel (*ca* 2g) was added to a stirred solution of 3-[2,(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl]-1*H*-indole-5-carbonitrile (4.98g) and sodium hypophosphite (10.06g) in pyridine (100ml), water (50ml) and acetic acid (50ml). The mixture was heated at *ca* 50° for 6h, periodically adding further Raney nickel (5 × *ca* 2g). After cooling, the mixture was filtered, and the filtrate was diluted with water (1250ml) and extracted with ethyl acetate (3 × 500ml). The combined organic extracts were washed with hydrochloric acid (2N; 2 × 500ml), dried (magnesium sulphate), evaporated *in vacuo*, and azeotroped with toluene (2 × 100ml), affording title aldehyde as a solid (4.6g). A sample (0.53g) was purified by chromatography on a silica column eluted with ethyl acetate, affording pure *title aldehyde* as a solid (0.49g), m.p. 202-3°.

Intermediate 14

(E) and (Z)-6[3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indol-5-yl]-5-hexenoic acid hydrate (4:5)

A solution of (4-carboxybutyl)triphenylphosphonium bromide (4.39g) in dry dimethylformamide (DMF; 40ml) was added dropwise over 3 min to a stirred suspension of potassium *tert*-butoxide (2.23g) in DMF (50ml) under nitrogen. The resulting suspension was stirred at room temperature for 15 min, a solution of Intermediate 13 (2.36g) in DMF (50ml) was added, and the resulting solution was heated at 100° for 44h. After allowing the emulsion to cool, it was partitioned between hydrochloric acid (2N; 1000ml) saturated with sodium chloride, and extracted with ethyl acetate (3 × 500ml). The combined organic extract was washed with water (4 × 500ml) and brine (500ml), dried (magnesium sulphate) and evaporated *in vacuo* to give a foam (5.98g). This was purified by flash chromatography on silica eluted successively with chloroform- methanol 49:1 (9000ml), 19:1 (1000ml), 9:1 (1000ml), affording *title acids* as a foam, collapsing to a gum (0.55g).

Analysis Found :	C,68.2;	H,5.3;	N,6.1
$C_{24}H_{22}N_2O_4.1.25H_2O$ requires :	C,67.8;	H,5.8;	N,6.6%

Intermediate 15

3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-hexanoic acid compound with ethanol (2:1)

A solution of Intermediate 14 (1.30g) in ethanol (170ml) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium oxide on charcoal (50% aqueous paste; 0.95g) for 1h, when hydrogen uptake (69ml) had ceased. The catalyst was filtered off, and the filrate was evaporated *in vacuo* to give the *title acid* as a solid (1.08g), m.p. 176-8°.

Intermediate 16

3-(Cyanomethyl)-N-[4-(methoxyphenyl)methyl]-1H-indole-5-propenamide

A mixture of N-[(4-methoxyphenyl)methyl] acrylamide (1.63g), 5-bromo-3-(cyanomethyl)-1*H*-indole (2g), palladium acetate (37mg), tri(o-tolyl) phosphine (109mg) and triethylamine (2ml) in acetonitrile (3ml) was heated at 100°C in a 'reactivial' for 72h. The cooled mixture was partitioned between ethyl acetate (3 × 25ml) and water (25ml) and the extracts dried ($MgSO_4$) and evaporated. The residue was triturated with dichloromethane-ethanol- ammonia solution (250:8:1) to give the *title compound* as a powder (1.4g) m.p. 108-110°C.

Example 1

3-(2-Aminoethyl)-N-[(4-methoxyphenyl)methyl]-1H-indole-5-propanamide, hemisuccinate hydrate (4:1)

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-[(4-methoxyphenyl)methyl]-1H-indole-5-propanamide*

A solution of Intermediate 2 (1.0g) in anhydrous THF (25ml) containing triethylamine (0.42ml) was treated with pivaloyl chloride (0.37ml) and stirred at 0° for 1h. A solution of 4-methoxybenzenemethanamine (0.387g) in anhydrous THF (10ml) was added and the mixture stirred at room temperature for 2.5h. The suspension was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was triturated with water (30ml) and extracted with ethyl acetate (2 × 50ml). The combined organic extracts were evaporated under reduced pressure to afford a solid (ca. 2.0g). Trituration with ether yielded a powder (0.8g) which was crystallised from butan-2-one/cyclohexane to present the *title compound* as a powder (0.49g) m.p. 196-199°.

(ii) *3-(2-Aminoethyl)-N-[(4-methoxyphenyl)methyl]-1H-indole-5-propanamide, hemisuccinate hydrate (4:1)*

A stirred suspension of the product of stage (i) (0.48g) in ethanol (10ml) containing hydrazine hydrate (0.1ml) was heated under reflux for 3h. Hydrazine hydrate (0.05ml) was added and the solution was heated under reflux for a further 1h. After cooling, the solution was evaporated to dryness under reduced pressure. The residue was mixed with 2N sodium carbonate solution (60ml), and extracted with methylene chloride (100ml). The extract was washed with 2N sodium carbonate (2 × 60ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a gum (0.25g). This material was chromatographed on a column of silica gel (eluants A and B), and evaporation of the appropriate fractions presented the free base as a gum (0.204g). A solution of this material in hot isopropanol (2ml) was treated with a hot solution of succinic acid (0.0343g) in isopropanol (2ml). On cooling the *title compound* crystallised as a powder (0.189g) m.p. 185-7°.

Analysis Found :	C,66.6;	H,7.0;	N,10.0;
$C_{21}H_{25}N_3O_2.0.5C_4H_6O_4.0.25H_2O$ requires :	C,66.5;	H,6.9;	N,10.1%

N.m.r. (250 MHz) δ(DMSO-d_6), includes 2.86-3.00 (6H,m,CH_2CH_2CO and ($CH_2CH_2NH_2$), 3.76 (3H,s,OCH_3), 4.22 (2H,d,CH_2NH), 6.96-7.10 (3H,m,H-6 and aromatics), 8.30 (1H,br.t,NHCO) and 10.84 (1H,br.s, indole N*H*).

The following compounds were prepared using a similar method to that in Example 1, with the appropriate amine starting material. Reaction conditions for stages (i) and (ii) are given in Tables 1 and 2 hereinafter, respectively.

Example 2

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-[4-(1-pyrrolidinyl)phenyl]-1H-indole-5-propanamide*

m.p. 197-9°.

(ii) *3-(2-Aminoethyl)-N-[4-(1-pyrrolidinyl)phenyl]-1H-indole-5-propanamide, hemisuccinate*

m.p. 222-3°.

Analysis Found :	C,68.8;	H,7.1;	N,12.6
$C_{23}H_{28}N_4O.O.5C_4H_6O_4$ requires :	C,68.9;	H,7.2;	N,12.9%

N.m.r. (90MHz) δ(DMSO-d_6), includes 1.90 (4H,m,pyrrolidine -CH_2CH_2N), 2.50-2.75 (2H,m,CH_2CH_2CO), 2.78-3.05 (6H,m,CH_2CH_2CO and $CH_2CH_2NH_2$), 5.80 (2H br.,NH_2), 7.10-7.50 (5H,m,aromatics), 9.65 1H,br.s,N*H*CO) and 10.70 (1H, br.s, indole N*H*).

Example 3

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-(phenylmethyl)-1H-indole-5-propanamide*
m.p. 142-3°.

(ii) *3-(2-Aminoethyl)-N-(phenylmethyl)-1H-indole-5-propanamide, hydrochloride*
m.p. 205-6°.
N.m.r. (90MHz) δ(DMSO-d_6), includes 2.80-3.10 (6H,m,C*H*$_2$CH$_2$CO and C*H*$_2$C*H*$_2$NH$_2$), 4.27 (2H,d,C*H*$_2$Ph), 8.45 (1H,br.t,N*H*CO) and 10.90 (1H,br.s, indole N*H*).

Example 4

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-(phenylmethyl)-1H-indole-5-butanamide*
m.p. 166-7°.

(ii) *3-(2-Aminoethyl)-N-(phenylmethyl)-1H-indole-5-butanamide, hydrochloride*
m.p. 195-8°.
N.m.r. (90MHz) δ(DMSO-d_6), includes 1.80 (2H,m,CH$_2$C*H*$_2$CH$_2$), 3.00 (4H,s,C*H*$_2$C*H*$_2$NH$_2$), 4.30 (2H,d,C*H*$_2$Ph), 7.1-7.40 (8H,m,aromatics), 8.40 (1H,t,N*H*CO) and 10.90 (1H, br.d, indole N*H*).

Example 5

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-(4-methoxyphenyl)-1H-indole-5-propanamide*
m.p. 184-6°.

(ii) *3-(2-Aminoethyl)-N-(4-methoxyphenyl)-1H-indole-5-propanamide, hydrochloride*
m.p. 264-66°.
N.m.r. (90MHz) δ(DMSO-d_6), includes 2.80-3.10 (6H,m.C*H*$_2$CH$_2$CO and C*H*$_2$C*H*$_2$NH$_2$), 3.70 (3H,s,OC*H*$_3$), 7.2-7.70 (5H,m, CO*NH* and aromatics) 8.20 (2H,br,N*H*$_2$) and 10.90 (1H,d,indole N*H*).

Example 6

(i) *N-[(4-Chlorophenyl)methyl]-3-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-propanamide*
m.p. 199.5-202°.

(ii) *3-(2-Aminoethyl)-N-[(4-chlorophenyl)methyl]-1H-indole-5-propanamide, hemisuccinate, hydrate (4:1)*
m.p. 188-192°.

Analysis found :	C,63.1;	H,6.05;	N,9.8
$C_{20}H_{22}ClN_3O.O.5C_4H_6O_4.O.25H_2O$ requires :	C,63.0;	H,6.1;	N,10.2%

N.m.r. (250MHz) δ(DMSO-d_6), includes 2.90 (6H,m,C*H*$_2$CH$_2$CO and C*H*$_2$C*H*$_2$NH$_2$), 4.25 (2H,d,C*H*$_2$Ph), 7.0-7.40 (7H,m,aromatics), 8.40 (1H,t,*NH*CO) and 10.80 (1H,br,s,indole N*H*).

Example 7

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-phenyl-1H-indole-5-butanamide*
m.p. 152-3°.

(ii) *3-(2-Aminoethyl)-N-phenyl-1H-indole-5-butanamide, hydrochloride*
m.p. 222-4°.
N.m.r. (90 MHz) δ(DMSO-d_6), includes 2.0 (2H,m,CH$_2$C*H*$_2$CH$_2$), 3.00 (4H,s,C*H*$_2$C*H*$_2$NH$_2$), 6.90-7.70 (9H,m,aromatics), 10.10 (1H,br.s,*NH*CO) and 10.90 (1H,br.s, indole N*H*).

Example 8

(i) *N-(4-Chlorophenyl)-3-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-propanamide*
m.p. 200-203°.

(ii) *3-(2-Aminoethyl)-N-(4-chlorophenyl)-1H-indole-5-propanamide hemisuccinate*
m.p. 216-218°.

Analysis found :	C,62.6;	H,5.8;	N,10.2.
$C_{19}H_{20}ClN_3O.0.5C_4H_6O_4$ requires :	C,62.9;	H,5.8;	N,10.5%

N.m.r. (250 MHz) δ(DMSO-d_6), 2.80-3.10 (6H,m,COCH$_2$C*H*$_2$ and C*H*$_2$C*H*$_2$NH$_2$), 7.35-7.50 (3H,m,aromatics), 10.20 (1H,br.s, N*H*CO) and 10.80 (1H,br.s,indole N*H*).

Example 9

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-[4-(aminocarbonyl)phenyl]-1H-indole-5-propanamide*
m.p. 238-240°.

(ii) *N-[4-(Aminocarbonyl)phenyl]-3-[2-(aminoethyl)]-1H-indole-5-propanamide compound with creatinine, sulphuric acid and water (1:1:1:1.5)*
m.p. 205-208°.

Analysis found : C,49.8; H,6.0; N,16.3;
$C_{21}H_{24}N_4O_2.C_4H_7N_3O.H_2SO_4.1.5H_2O$ requires : C,49.8; H,6.0; N,16.3%

N.m.r. (250 MHz) δ(DMSO-d_6), 2.90-3.20 (9H, m and s, CH_2CH_2CO and $CH_2CH_2NH_2$), 4.30 (2H,d,CH_2NHCO), 7.20-8.00 (9H,m,aromatics and CONH$_2$), 8.40 (1H,t,NHCO) and 10.90 (1H,br.s,indole NH).

Example 10

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-N-[4-(1-pyrrolidinyl)phenyl]methyl]-1H-indole-5-propanamide*

m.p. 121-123°.

(ii) *3-(2-aminoethyl)-N-[[4-(1-pyrrolidinyl)phenyl]methyl]-1H-indole-5-propanamide, hemisuccinate*

m.p. 206-208°.

Analysis found : C,69.3; H,7.4; N,12.3;
$C_{24}H_{30}N_4O.0.5C_4H_6O_4$ requires : C,69.5; H,7.4; N,12.5%

N.m.r. (250 MHz) δ(DMSO-d_6), includes 2.00 (4H;m,pyrrolidine-CH_2CH_2N), 2.80-3.00 (6H,m,CH_2CH_2CO and $CH_2CH_2NH_2$), 3.20 (4H,m,pyrrolidine -CH_2CH_2N), 4.15 (2H,d,CH_2NHCO), 6.40-7.00 (5H,m,aromatics and H-6), 8.20 (1H,t,NHCO) and 10.90 (1H,br.s,indole, NH).

Example 11

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-(2-propenyl)-1H-indole-5-propanamide*

m.p. 268-9°.

(ii) *3-(2-Aminoethyl)-N-(2-propenyl)-1H-indole-5-propanamide, hydrochloride*

m.p. 230-1°.

Analysis found : C,62.3; H,7.3; N,13.5;
$C_{16}H_{21}N_3O.HCl$ requires : C,62.4; H,7.2; N,13.7%

N.m.r. (250 MHz) δ(D_2O), includes 3.10 (2H,t,CH_2CH_2CO), 3.35 (2H,t,$CH_2CH_2NH_2$), 3.70 (2H,m,NHCH_2CH=), 4.90 (-,m,CH=CH_2) and 5.70 (1H,m,CH_2CH=CH_2).

TABLE I

	Activation				*acylation*				
Ex No.	*Indole (g)*	*TEA (ml)*	*PC (ml)*	*time*	*amine (g)*	*time*	*temp °C*	*crystallisation solvent*	*yield (g)*
2(i)	1.0	0.42	0.37	10 min	0.45	2h	-	EtOH	0.98
3(i)	1.0	0.42	0.37	10 min	0.29	15 min	-	IPAC/CH	1.0
4(i)	1.04	0.42	0.37	20 min	0.29	20 min	RT	MeOH/IPAC	0.84
5(i)	1.5	0.63	0.56	10 min	0.51	1.5h	-	IPAC/MeOH	1.1
6(i)	1.0	0.42	0.37 +0.037	1h +0.5h	0.39	20h	RT	BU/CH (×2)	0.47
7(i)	1.04	0.42	0.37	20 min	0.25ml	18h	RT	IPAC	0.78
8(i)	1.5	0.63	0.55	1h	0.52	20h	RT	BU/CH	0.81
9(i)	1.5	0.63	0.56	10 min	0.54	(2h (2h	RT) reflux)	AC/IPA	0.49
10(i)	1.5	0.63	0.55	2h	0.72	18h	RT	EtOAC	0.6
11(i)	1.0	0.42	0.37	10 min	0.16	2h	-	IPA/IPAC	0.89

TABLE 2

Ex No.	Indole (g)	HH (ml)	time (h)	eluant	salt formation: base (g)	salt formation: acid (g)	salt formation: solvent	crystallisation solvent	yield (g)
2(ii)	0.75	0.8	8	C	-	Succinic, MeOH (0.176)		-	0.49
3(ii)	0.9	0.2	2	-	-	HCl/MeOH (2N, 2ml)		IPA/IPAC (1:1)	0.48
4(ii)	0.8	0.2 +0.2	1.5 +2	D	-	HCl/EtOH (3.1N, 0.6ml)		IPA/IPAC (1:1)	0.53
5(ii)	1.0	0.43	3	C	0.25	HCl/EtOH (3.1N, 0.3ml)		IPA/IPAC (1:1)	0.205
6(ii)	0.59	0.12	2.5	A+B	0.152	succinic, IPA (0.025)			0.125
7(ii)	0.75	0.25	2	E		HCl/EtOH (3.1N, 0.6ml)		MeOH/IPAC (1:2)	0.48
8(ii)	0.79	0.16 +0.08	2 +2	F,G+C	0.49	succinic, IPA (0.085) MeOH IPAC		-	0.345
9(ii)	0.22	0.07	3	C	0.115	creatinine + H_2SO_4 aq. EtOH		-	0.119
10(ii)	0.4	0.12	3	C	0.3	succinic, IPA (0.09)			0.25
11(ii)	0.85	0.20	1	-	-	HCl/MeOH (2N, 2ml) EtOH		EtOH/IPAC (1:1)	0.57

Example 12

3-(2-Aminoethyl)-1H-indole-5-propanamide, compound with creatinine sulphate, sulphuric acid and water (1:1:1:1.25)

Ethyl 3-(2-aminoethyl)-1*H*-indole-5-propanoate (0.3g) was heated at 38° for 24h in 0.880 d ammonia (20ml). Evaporation to dryness gave the crude amide which was purified by chromatography (eluant J) to give an oil (130mg). This was dissolved in ethanol and an aqueous solution 1 molar in sulphuric acid and creatinine (0.28ml) added. Addition of acetone to the hot (80°) creatinine sulphate solution until cloudy gave the *title compound* as a solid (120mg) m.p. 218-220° dec.

Analysis found :	C,44.4;	H,6.05;	N,17.7;
$C_{13}H_{17}N_3O.C_4H_7N_3O.H_2SO_4 1.25H_2O$ requires :	C,44.1;	H,6.2;	N,18.1%

Example 13

3-(2-Aminoethyl)-N-methyl-1H-indole-5-propanamide, hydrochloride

To a solution of Intermediate 2 (1.0g) in dry tetrahydrofuran (25ml) containing triethylamine (0.42ml) at 0°C was added pivaloyl chloride (0.37ml). After stirring for 10 mins the suspension was filtered and the filtrate evaporated under reduced pressure. 33% Ethanolic methylamine (20ml) was added to the oily residue and the resulting solution was stirred for 18h. Evaporation of the solvent gave a solid which was partitioned between 2N hydrochloric acid (10ml) and ethyl acetate (25ml). The organic phase was separated and again extracted with 2N hydrochloric acid (10ml). The combined aqueous extracts were saturated with potassium carbonate and extracted with ethyl acetate (4×50ml). Evaporation of the dried

(Na_2SO_4) combined extracts gave a solid which was dissolved in 2N methanolic hydrochloric acid (10ml) and again evaporated to dryness. Crystallisation of the residue from propan-2-ol and isopropyl acetate [2:1] (10ml) gave the title compound (0.27g) m.p. 224-6°.

Analysis Found :	C,59.3;	H,7.2;	N,14.6;
$C_{14}H_{19}N_3O.HCl$ requires :	C,59.7;	H,7.2;	N,14.9%

N.m.r. (90 MHz) δ(DMSO-d_6), includes 2.90 (2H,m,C*H*$_2$CH$_2$CO), 3.10 (4H,br.s,C*H*$_2$C*H*$_2$NH$_2$), 7.10-7.50 (3H,m,aromatics), 7.80 (1H,q,N*H*CH$_3$), 8.20 (2H,br,N*H*$_2$) and 11.00 (1H,br.s, indole N*H*).

Example 14

3-[2-(Dimethylamino)ethyl]-N-[(4-methoxyphenyl)methyl]-1H-indole-5-propanamide hydrochloride

To a stirred solution of the product of Example 1(ii) (0.2g) in n-propanol (5ml) at 0° was added formaldehyde solution (37-40% aqueous, 0.26ml) and the mixture stirred for 15min. Sodium borohydride (0.11g) was added portionwise over 5min, keeping the temperature at 0°. After 30min the mixture was acidified with hydrochloric acid (2N, 5ml) and diluted with water (25ml). The solution was washed with ethyl acetate (2×10ml) and then basified with sodium carbonate (2N, 8ml). The cloudy solution was extracted with ethyl acetate (3×25ml) and the extracts evaporated under reduced pressure. The residue (0.2g) was chromatographed on silica (G) to give an oil (45mg). This oil was dissolved in absolute ethanol (2ml) and ethereal hydrogen chloride solution (5ml) was added. Ethyl acetate (15ml) was then added and the resulting solid collected and dried to give the *title compound* as a powder (37mg) m.p. 94-96°.

Analysis found :	C,64.2;	H,7.3;	N,9.1;
$C_{23}H_{29}N_3O_2.HCl.0.6CH_3CH_2O_2CH_3$ requires :	C,64.5;	H,7.6;	N,9.1%

N.m.r. (250 MHz) δ(DMSO-d_6), includes 2.80 (6H,s,N*Me*$_2$), 2.95 (2H,t,C*H*$_2$CH$_2$CO), 3.00-3.30 (4H,m,C*H*$_2$C*H*$_2$NMe$_2$), 3.70 (3H,s,OC*H*$_3$). 4.20 (2H,d,C*H*$_2$NHCO), 7.0-7.50 (6H,m,aromatics), 8.30 (1H,t,N*H*CO) and 10.90 (1H,br.s, indole N*H*).

Example 15

3-[2-(Dimethylamino)ethyl]-1H-indole-5-propanamide oxalate

Intermediate 12 (1.54g) was heated in a capped glass bottle with 880 ammonia (1ml) and methanol (1.2ml) at 75° for 26h. Methanol was partly evaporated off, more 880 ammonia (1ml) was added, and heating was continued at 75° for 24h. Evaporation of the solvent gave a foam (1.32g) which was purified by flash chromatography (eluant L) to give an oil (0.507g). A portion (481mg) of this was dissolved in methanol (2ml), and oxalic acid (175mg) in methanol was added. Addition of dry ether gave a gummy precipitate, which was triturated with dry ether to give the *title compound* as a solid (0.401g), m.p. 139-142°.

Analysis found :	C,58.1;	H6.8;	N,11.7;
$C_{15}H_{21}N_3O.C_2H_2O_4$ requires :	C,58.4;	H,6.6;	N,12.0%

N.m.r (90MHz) δ(DMSO-d_6), includes 2.7-3.40 (12H,m,C*H*$_2$CH$_2$CO, C*H*$_2$C*H*$_2$NH$_2$ and N*Me*$_2$), 6.70 (1H,br.s,CON*H*H), 7.10-7.50 (4H,m,aromatics and CONH*H*) and 10.90 (1H,br.s,indole N*H*).

Example 16

3-[2-(Dimethylamino)ethyl]-N,N-dimethyl-1H-indole-5-propanamide succinate

A mixture of dimethylamine in ethanol (33% w/v; 4ml) and Intermediate 12 (0.75g) was heated in a 'reactavial' at 100°C for 24h. The solution was then evaporated under reduced pressure and the residue chromatographed on silica (F and G) to give an oil (0.112g). This oil was dissolved in hot isopropanol (2ml) and a solution of succinic acid (46mg) in hot isopropanol added. Isopropyl acetate was added dropwise to the hot mixture until a cloudy solution was obtained. The solid obtained on cooling was recrystallised from isopropanol to give the *title compound* as a powder (75mg) 131-133°.

N.m.r. (90 MHz) δ(DMSO-d_6), includes 2.40 2.7-3.40(12H,m,C*H*$_2$CH$_2$CO, C*H*$_2$C*H*$_2$NH$_2$ and N*Me*$_2$), 6.70 (1H, br.s, CON*H*H), 7.10-7.50 (4H,m,aromatics and CONH*H*) and 10.90 (1H, br.s, indole N*H*).

Analysis found :	C,61.4;	H,8.0;	N,9.8.
$C_{17}H_{25}N_3O.C_4H_6O_4.0.25H_2O$ requires :	C,61.5;	H,7.7;	N,10.2.

N.m.r (250 MHz) δ(DMSO-d_6), includes 2.80-3.00 (14H,m,N*Me*$_2$, CON*Me*$_2$ and C*H*$_2$CH$_2$CO), 3.00-3.40 (4H,m,C*H*$_2$C*H*$_2$NMe$_2$) and 10.90 (1H,br.s, indole N*H*).

Example 17

3-[2-(Dimethylamino)ethyl]-N-methyl-1H-indole-5-propanamide hydrochloride

A mixture of methylamine in ethanol (33% w/v, 4ml) and Intermediate 12 (0.56g) was heated in a 'reactivial' at 75°C for 24h. The cooled solution was evaporated under reduced pressure and the residue chromatographed on silica (M and F) to give an oil (220mg). This oil was dissolved in ethanolic hydrogen chloride (5ml) and the solution evaporated under reduced pressure to give a gum. Trituration of the gum with ethyl acetate (ca 15ml) gave a solid which was collected and dried (0.18g) m.p. 73-75°.

Analysis found :	C,58.4;	H,7.9;	N,12.4.
$C_{16}H_{23}N_3O.HCl.H_2O$ requires :	C,58.6;	H,7.9;	N,12.8%.

N.m.r. (250 MHz), δ(DMSO-d_6), includes 2.60 (3H,d,NHC*H*$_3$), 2.85 (6H,s,N*Me*$_2$), 2.90 (2H,t,C*H*$_2$CH$_2$CO), 3.10-3.40 (4H,m,C*H*$_2$C*H*$_2$NMe$_2$), 7.90 (1H,br,q,N*H*CH$_3$) and 10.90 (1H,br.s, indole N*H*).

Example 18

(i) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-hexanamide*

Pivaloyl chloride (0.38ml) was added to a solution of Intermediate 15 (1.31g) and triethylamine (0.43ml) in dry tetrahydrofuran (100ml), and the mixture was stirred at room temperature for 1h, adding further triethylamine (0.10ml) and pivaloyl chloride (0.05ml) after 40 min. A saturated solution of ammonia in tetrahydrofuran (60ml) was added, and the mixture was stirred at room temperature in a sealed flask for 3.5h. The mixture was filtered, and the filtrate was evaporated *in vacuo* to give an oil, which was partitioned between sodium carbonate solution (2N; 150ml) and ethyl acetate (3×100ml). The combined organic extract was dried (magnesium sulphate) and evaporated *in vacuo* to give a solid (0.99g). This material was partially purified by flash chromatography eluted with ethyl acetate-methanol (19:1) to give a solid (0.84g). A sample of this material (0.117g) was suspended in water (10ml) for 1h at 90°. The precipitate was filtered off, washed with boiling water (5ml), and dried *in vacuo* at 50° to give the *title compound* as a solid (0.075g), m.p. 177-9°.

(ii) *3-(2-Aminoethyl)-1H-indole-5-hexanamide, compound with creatinine, sulphuric acid, water and ethanol (10:10:10:5:2)*

A mixture of the product of stage (i) (0.59g), hydrazine hydrate (1.5ml) and ethanol (50ml) was heated at reflux for 1.75h, allowed to cool, and evaporated to dryness. The resulting solid was azeotroped with absolute ethanol (2×50ml), and was then partitioned between sodium carbonate (2N; 50ml) and ethyl acetate (3×50ml). The combined organic extract was dried (magnesium sulphate) and evaporated *in vacuo* to give the title base as an oil (0.43g). The oil was dissolved in a hot mixture of ethanol (48ml) and water (6ml), and was treated with an aqueous solution of creatinine and sulphuric acid (1:1, 2M; 0.75ml). On cooling, the *title compound* crystallised as a solid (0.49g) m.p. 188-93° (dec).

Analysis found :	C,49.0;	H,7.1;	N,16.8;
$C_{16}H_{23}N_3O.C_4H_7N_3O.H_2SO_4.0.5H_2O.0.2C_2H_6O$ requires:	C,48.7;	H,6.9;	N,16.7%

N.m.r. (90 MHz) δ(DMSO-d_6) includes 1.20-1.80 (6H,m,-CH$_2$(C*H*$_2$)$_3$CH$_2$-), 2.10 (2H,t,CH$_2$C*H*$_2$CO), 2.90 (3H,s,NC*H*$_3$), 3.00 (4H,br.s,C*H*$_2$C*H*$_2$NH$_2$) and 10.90 (1H,brs, indole N*H*).

Example 19

3-[2-(Dimethylamino)ethyl]-N-(2-propenyl)-1H-indole-5-propanamide oxalate

A mixture of Intermediate 12 (0.75g) and allylamine (3.5ml) in methanol (1.5ml) was stirred at room temperature in a 'reactivial' for 96h. The solvent was evaporated under reduced pressure and the residue chromatographed on silica (eluant N). Appropriate fractions were collected and evaporated under reduced pressure to give an oil (0.142g), which was dissolved in methanol (2ml) and a solution of oxalic acid (44mg) in methanol (1ml) added. Ethyl acetate (ca. 20ml) was added and the resulting solid collected and dried to give a powder (0.13g) m.p. 68-70°.

Analysis found :	C,60.8;	H,7.5;	N,10.2.
$C_{18}H_{25}N_3O.(CO_2H)_2.0.33$ EtOAc requires :	C,61.2;	H,7.1;	N,10.0%

Example 20

(i) *3-(Cyanomethyl)-N-[4-(methoxyphenyl)methyl]-1H-indole-5-propanamide*

A solution of Intermediate 16 (1.4g) in methanol (50ml) was added to a pre-reduced suspension of 10% palladium oxide on charcoal (50% paste with water, 300mg) in methanol (20ml) and the mixture hydrogenated until uptake had ceased (ca 95ml). The catalyst was removed by filtration and the filtrate evaporated under reduced pressure to give an oil (1.2g).

T.l.c. (M) Rf 0.40, detection u.v/$KMnO_4$.

(ii) *3-[2-(Ethylamino)ethyl]-N-[4-(methoxyphenyl)methyl]-1H-indole-5-propanamide oxalate salt*

A mixture of the product of stage (i) (0.6g) and ethanolic ethylamine solution (30ml 30% w/v) in ethanol (100ml) was added to a prereduced suspension of 10% palladium oxide on charcoal (50% paste with water 0.6g) and the mixture hydrogenated until uptake ceased. A further quantity of catalyst (0.6g) was added and the mixture hydrogenated again until uptake ceased. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure to give an oil (0.59g). This oil was dissolved in methanol (2ml) and a solution of oxalic acid (140mg) in ethyl acetate (5ml) added. The solution was diluted with ethyl acetate (ca 50ml) and the resulting solid collected, washed well with diethyl ether (ca 25ml) and dried to give the *title compound* as a powder (0.47g) m.p. 104-6°C.

Analysis found :	C,62.6;	H,6.8;	N,8.8;
$C_{23}H_{29}N_3O_2.(CO_2H)_2.0.5H_2O$ requires :	C,62.8;	H,6.7;	N,8.8%

Water assay shows 0.4mol water.

The following examples illustrate pharmaceutical formulations according to the invention, containing 3-(2-aminoethyl)-*N*-[(4-methoxyphenyl)methyl]-1*H*-indole-5-propanamide hemisuccinate hydrate (4:1) as the active ingredient. Other compounds of the invention may be formulated in a very similar manner.

Tablets for oral administration
Direct compression

	mg/tablet
Active ingredient	8.4
Calcium hydrogen phosphate B.P.*	89.1
Croscarmellose sodium USP	2.00
Magnesium stearate, B.P.	0.50
Compression weight	100mg

* of a grade suitable for direct compression

The active ingredient is sieved before use. The calcium hydrogen phosphate, croscarmellose sodium and active ingredient are weighed into a clean polythene bag. The powders are mixed by vigorous shaking then the magnesium stearate is weighed and added to the mix which is blended further. The mix is then compressed using a Manesty F3 tablet machine fitted with 5.5mm flat bevelled edge punches, into tablets with target compression weight of 100mg.

Tablets may also be prepared by other conventional methods such as wet granulation.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Capsules

	mg/capsule
Active ingredient	8.4
*Starch	190.6
Magnesium Stearate BP	1.00
Fill Weight	200.00

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No.2 hard gelating capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

Syrup

		mg/5ml dose
Active ingredient		8.4
Buffer)		
Flavour)		
Colour)		as required
Preservative)		
Thickening agent)		
Sweetening agent)		
Purified Water	to	5.00ml

The active ingredient, buffer, flavour, colour, preservative, thickening agent and sweetening agent are dissolved in some water, the solution is adjusted to volume and mixed. The syrup produced is clarified by filtration.

Suppository for rectal administration

Active ingredient		8.4mg
* Witepsol H15	to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

Injection for intravenous administration

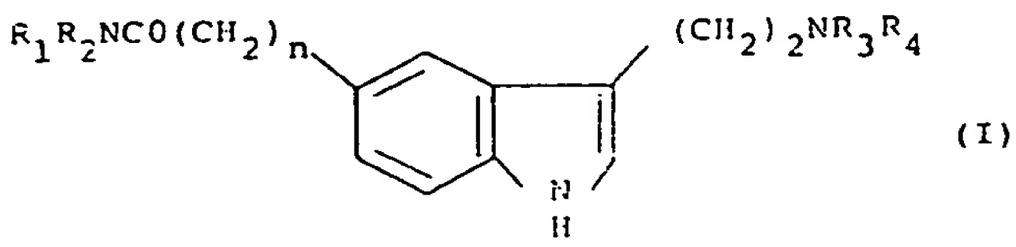
		mg/ml
Active ingredient		2.1
Sodium Chloride BP		as required
Water for Injection BP	to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

CLAIMS

1. Indoles of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom, C_{1-6} alkyl, C_{3-7} cycloaklyl or C_{3-6} alkenyl group, or a phenyl or phenyl (C_{1-4}) alkyl group in which the phenyl ring may be unsubstituted or substituted by one or two substituents selected from C_{1-3} alkoxy, hydroxy, halogen, a group R_5R_6NCO- where R_5 and R_6 (which may be the same or different) each represents a hydrogen atom or a C_{1-3} alkyl group, or a group R_7R_8N-, where R_7 and R_8 (which may be the same or different) each represents a hydrogen atom or a C_{1-3} alkyl group, or R_7R_8N- represents a saturated monocyclic 5- to 7-membered ring;

R_2 represents a hydrogen atom or a C_{1-6} alkyl group; or

R_1 and R_2 together with the nitrogen atom to which they are attached form a saturated monocyclic 5- to 7-membered ring;

R_3 and R_4 which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group, or a 2-propenyl group; and

n is an integer from 2 to 5;

and physiologically acceptable salts and solvates thereof.

2. Indoles according to Claim 1, wherein R_1 represents a hydrogen atom, a C_{1-6} alkyl or C_{3-6} alkenyl group, or a phenyl or phenyl (C_{1-4}) alkyl group in which the phenyl ring may be unsubstituted or substituted by one or two substituents as defined in Claim 1.

3. Indoles according to Claim 1 or 2, wherein one of R_1 and R_2 represents a hydrogen atom.

4. Indoles according to any of Claims 1 to 3, wherein R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

5. Indoles according to any of Claims 1 to 4, wherein n is 2 or 3.

6. Indoles according to Claim 1, wherein R_1 represents a C_{1-3} alkyl group, a C_{3-6} alkenyl group or a phenyl (C_{1-2}) alkyl group, in which the phenyl ring may be unsubstituted or substituted by one or two substituents as defined in Claim 1; R_2 represents a hydrogen atom; R_3 and R_4, which may be the same or different, each represents a hydrogen atom or a methyl or ethyl group; and n is 2 or 3.

7. Indoles according to Claim 1, selected from

3-(2-aminoethyl)-*N*-(phenylmethyl)-1*H*-indole-5-propanamide;

3-(2-aminoethyl)-*N*-([4-(1-pyrrolidinyl)phenyl]methyl)-1*H*-indole-5-propanamide;

3-[2-(dimethylamino)ethyl]-N-[(4-methoxyphenyl)methyl]-1*H*-indole-5-propanamide;

3-(2-aminoethyl)-*N*-(2-propenyl)-1*H*-indole-5-propanamide; and

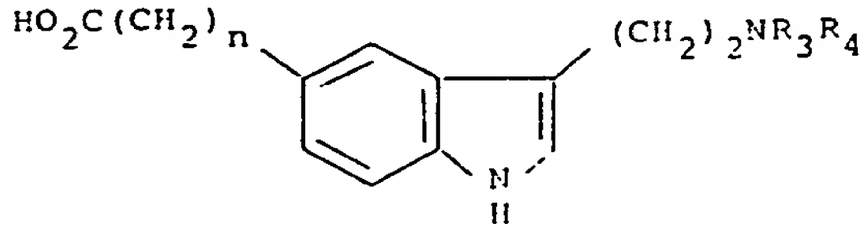
3-(2-aminoethyl)-*N*-[(4-methoxyphenyl)methyl]-1*H*-indole-5-propanamide;

and the physiologically acceptable salts and solvates thereof.

8. A pharmaceutical composition which comprises, as active ingredient, an effective amount of at least one indole of general formula (I) according to Claim 1 or a physiologically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers or excipients.

9. A process for the preparation of an indole of general formula (I) according to Claim 1 or a salt or solvate thereof which comprises:

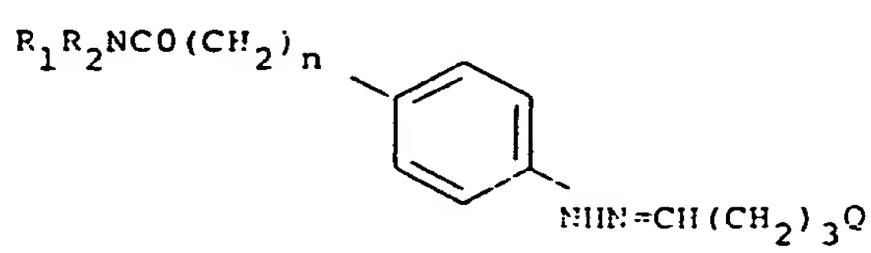
(A) condensing an amine of formula R_1R_2NH (where R_1 and R_2 are as defined in Claim 1) with an acid of general formula (II):



(II)

(where R_3, R_4 and n are as defined in Claim 1) or an acylating agent corresponding thereto, or a salt or a protected derivative thereof; or

(B) cyclising a compound of general formula (III):

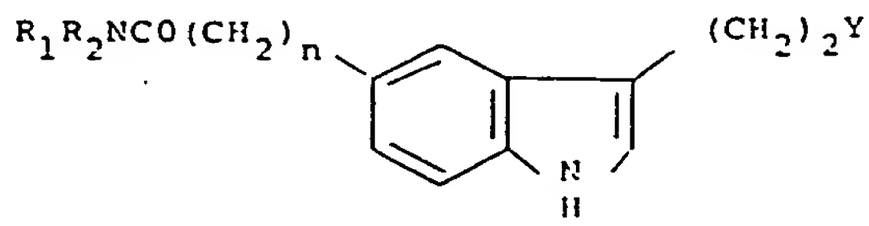


(III)

(wherein R_1, R_2 and n are as defined in Claim 1 and Q is the group NR_3R_4 (where R_3 and R_4 are as defined in Claim 1)

or a protected derivative thereof or a leaving group; or

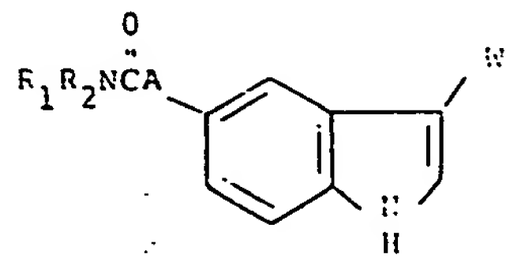
(C) reacting a compound of general formula (VI):



(VI)

(wherein R_1, R_2 and n are as defined in Claim 1 and Y is a readily displaceable group) or a protected derivative thereof, with an amine of formula R_3R_4NH (where R_3 and R_4 are as defined in Claim 1); or

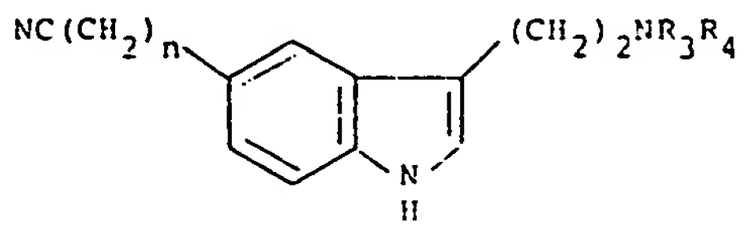
(D) reducing a compound of general formula (VII):



(VII)

(wherein R_1 and R_2 are as defined in Claim 1 and W is a group capable of being reduced to give the required $-(CH_2)_2NR_3R_4$ group or a protected derivative thereof (where R_3 and R_4 are as defined in Claim 1) and A represents the group $-(CH_2)_n-$ or a group capable of being reduced to $-(CH_2)_n-$ (where n is as defined in Claim 1), or a salt or protected derivative thereof; or

(E) reacting a nitrile of general formula (IX):



(IX)

(wherein R_3, R_4 and n are as defined in Claim 1) or a salt or protected derivative thereof, with a suitable oxygen-containing compound; or

(F) converting a compound of general formula (I) as defined in Claim 1, or a salt or protected derivative thereof into another compound of general formula (I); or

(G) subjecting a protected derivative of general formula (I) as defined in Claim 1 or a salt thereof to a reaction to remove the protecting group or groups; and if necessary and/or desired effecting one or two additional reactions subsequent to any of processes A to F comprising:-

(i) removing any protecting group or groups; and

(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

Printed in the UK for HMSO, D8818935, 4/86, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.